ELECTROPHYSIOLOGICAL CONNECTIONS BETWEEN MESENCEPHALIC CENTRAL GRAY MATTER AND CEREBRAL CORTEX

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ELECTROPHYSIOLOGICAL CONNECTIONS BETWEEN MESENCEPHALIC CENTRAL GRAY MATTER AND CEREBRAL CORTEX

by

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(Received for publication Oct. 30, 1958)

INTRODUCTION

In our laboratory we have studied the problem of unconsciousness due to head injury clinically and experimentally for many years and found that in unanesthetized (restrained) animal brain portions which play an important role in bringing about coma (loss of nociceptive reflex) are mesencephalic central gray matter, medullary reticular formation and some other brain stem regions. If coma is associated, as supposed in a common sense, with loss of the functions of the whole cerebral cortex, we have to expect the existence of electrophysiological connections between these brain stem regions and diffuse cerebral cortex. Previously, ARAKI, SAKATA and MATSUNAGA suggested this possibility in the report "Recruiting Response-like EEG Changes Induced with Extrathalamic Stimulation of Cat."

On the other hand, according to the literature, there are definite thalamic regions which have electrophysiological connections with the diffuse cerebral cortex and many investigations have been made about recruiting response occurring through these connections since MORISON and DEMPSEY. The ascending activating system and the limbic system are thought to maintain the background activity of consciousness and these parts have been shown to have many neural connections from nearly all upper cerebral levels as well as from peripheries.

This study concerns with the connections of mesencephalic central gray matter with cerebral cortex and subcortical structures of unanesthetized (restrained) animals.

METERIALS AND METHODS

Unanesthetized cats weighting 1.7 to 4.0 kilograms were used. Trephination of the skull and installation of the stereotaxic instrument were carried out under ether anesthesia. The further experimental procedures were performed at least 2 hours after cessation of anesthesia. Some anesthetized cats were used as controls. Anesthesia was by means of intraperitoneal injection of Ravonal (sodium 5-ethyl-5-(1-methylbutyl) thiobarbiturate).

Observations of the responses to electric stimulations in unanesthetized (restrained) animal were performed when the animal was relaxed and spontaneous electroencephalogram was not activated. Stimulating electrode was bipolar electrode (the bared tip separated by a distance of 0.1 mm) consisting of two parallel steel wires with a diameter of 0.3 mm insulated with laquer except for 0.2 mm at the tips. In some cases, bipolar concentric electrode made of hypodermic needles (tip exposure of 0.5 mm) was used. Leading for surface EEG was through monopolar steel needles inserted through the skull to the level of dura or bipolar small silver ball electrodes with a diameter of 1 to 2 mm (tip distance of 2 to 4 mm) disposed gently on pia or dura. For each example, responses were recorded from more than six places of the whole convexity of the cerebral cortex. Deep EEG was recorded by means of the leading electrode consisting of the above mentioned steel wire monopolarly (tip exposure of 1 mm) and otherwise bipolarly (tip separated by a distance of 2 mm). In some instances, also concentric electrode was used.

Fig. 1 An example showing the tracts made by small stimulating electrode within mesencephalic central gray matter. To determine correct loci of tips of electodes, KLÜVER-BARRERA's stain and iron reaction (TIRMANN-SCHMELZER'S method) were carried out.

Indifferent electrode in the monopolar leading was placed on the nasal bone.

Stimulation (pulse duration : 0.2-1 msec., frequency : single shock to 30 per second, mainly about 10 per second, intensity : 0.5-40 volts) was delivered from a square wave stimulator (Nihon Koden Co.). The electrodes were inserted deeply, oriented with the HORSLEY-CLARKE'S stereotaxic apparatus, into mesencephalic medial portions, many thalamic nuclei and the other subcortical portions. The observation and recording of EEG were made with the 2 channel (Sanei) or 8 channel (Ediswan) apparatus and cathode ray oscillograph made to sweep at the moment of stimulation; for the latter a serial photographic apparatus was devised in our laboratory.

During the experimental procedure, especially long lasting procedure, it is necessary to take care of the state of the brain against cooling, dehydration and anoxia. Therefore, in order to maintain physiological conditions of the brain as well as possible, keeping an animal warm, attentative operative procedures and dropping down of warm physiological salt solution etc. were carried out.

At the end of experiment, after electrolysis was made at the locations of tips of deep elect-

rodes, brain was taken out immediately and fixed with ten percent formalin and afterwards locations of the tips of electrodes were ascertained histologically by means of KLÜVER-BARRERA's staining and iron reaction (TIRMANN-SCHMELZER's method). Anatomical guide of cat's brain was referred from H. JASPER and C. AJMONE-MARSAN (1954), WINKLER and POTTER (1914) and J. JIMNEZ-CASTELLANOS (1949).

RESULTS OF EXPERIMENT

(A) Electrophysiological connections between mesencephalic central gray matter and cerebral cortex.

(1) Mesencephalic regions, the stimulation of which induce diffuse cortical responses.

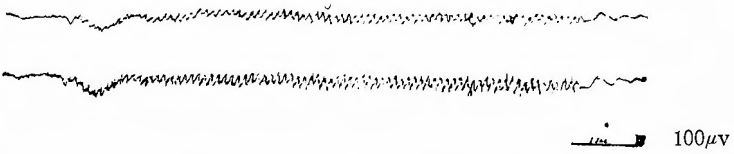

Fig. 2 An example of ink writer oscilloscope record of our response in bilateral anterior sigmoid gyrus following stimulation of mesencephalic central gray matter (1 msec., 15 v., 10 p.s.).

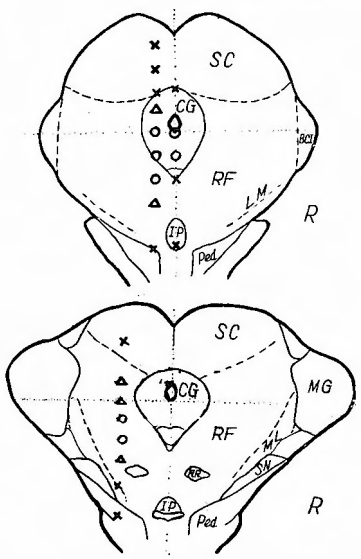

Fig. 3 Schematic diagram of paths through which stimulating electrode was inserted repeatedly into mesencephalon. Open circles indicate the points, stimulations of which yield marked response in diffuse cortical areas synchronized with each stimulus. Triangles indicate unstable or not so marked response. Crosses indicate no response in diffuse cortical areas following each stimulus.

After fixing the cat in the stereotaxic apparatus, stimulating electrode was dorsoventrally inserted step by step into the mesencephalon, at the level from the oculomotor nucleus to the trochlear nucleus, stimulation with supraliminal intensity and low frequency being given though it at each step, and induced responses on the surface EEG from each cortical region were recorded. Fig. 3 shows an example, in which directions of repeated insertions of electrode were: colliculus superior→mesencephalic reticular formation→lemniscus medialis→pyramidal tract, and colliculus superior→mesencephalic central gray matter→mesencephalic reticular formation→nucl. interpeduncularis, etc. In this case, stimulation of mesencephalic central gray matter, particularly its ventral portion, and the part of mesencephalic reticular formation adjacent to it induced distinct responses synchronized with each stimulus in the diffuse cortical areas. These areas of effective stimulation extend in mesencephalic transverse plane mostly, as seen in Fig. 3, 3 to 4 mm wide in ventrodorsal direction and their extent does

not necessarily correspond with the particular anatomical structures. When the stimulating electrode was more deeply inserted, the nearer it advanced through the mesencephalic reticular formation to the medial lemniscus, the more predominant responses appeared only in the anterior cerebral cortex.

Namely, mesencephalic regions, from which widespread synchronized cortical responses were induced by stimulation, especially typically with about 10 p s. repetitive stimuli, consisted of mesencephalic central gray, especially its ventral portion, and a part of mesencephalic reticular formation adjacent to it. It was difficult to determine the exact extent of these regions in our experiment and whenever we stimulated any point within this region, uniform cortical responses were obtained.

ARAKI, SAKATA and MATSUNAGA reported previously about these cortical responses (they called recruiting response-like EEG changes) that the responses appeared at a high rate by the stimulation of the mesencephalic central gray matter and adjacent reticular formation.

Generally, on stimulating the border of these regions, elicited responses were sometimes unstable and irregular and predominant in anterior cortical region with some variation in form. Wave form will be described later in detail. By stimulations of lemniscus medialis, nucl. interped., pyramidal tract and colliculus superior, there did not appear widespread cortical responses synchronized with each repetitive stimulus.

(2) Wave form of our response.*

Wave form of our cortical response is not easy to discuss owing to the mixtures of the spontaneous EEG and the complicated conditions of the animals, especially of their cortex, but the obtained responses are shown in Fig. 4 and Fig. 5. Generally, according to the stimulating point within the effective mesencephalic region the differences in wave form of cortical responses could not be found.

Our response showed mostly monophasic wave form, which was surface-negative, slowly appearing after the stimulus, but sometimes also triphasic form. The latter consists of an unstable little negative wave, appearing immediately after the shock artifact, then the mostly not remarkable slow positive wave following it and finally the most eminent large negative wave. Generally, initial negative wave and following positive wave are not so marked but the slowly appearing negative wave is usually the main component of our response. But the nearer to the sensory paths in the ventral mesencephalic reticular formation was the stimulating point and the more anterior the leading cortical area, the more remarkable became the initial negative wave and sometimes spike-like.

The main negative wave is the most reliable deflection, which shows long latency, the highest voltage (in our conditions, mostly 100 to 200 μv) and the longest duration. Its wave form and voltage usually does not tend to vary according to the cortical leading regions. On the contrary, the short latency, short duration and spike-like responses to stimulation of mesencephalic medial lemniscus were obtained from

* In this paper, it means diffuse synchronized cortical response to repetitive stimulation of mesencephalic central gray matter and its neighborhood in unanaesthetized (restrained) animals.

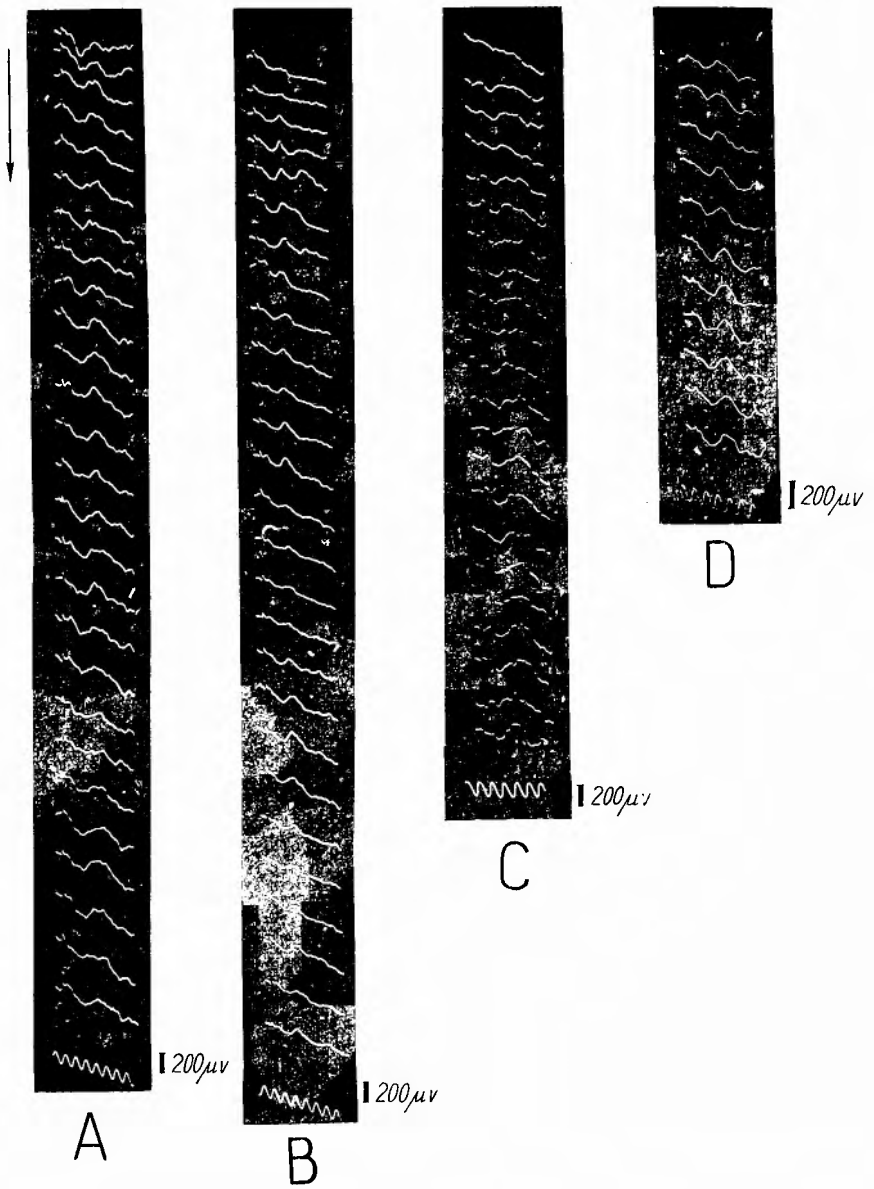

Fig. 4 Cortical responses induced with low frequency repetitive stimulation of mesencephalic central gray matter. A: Stimulation (0.3 msec., 10v., 8 p.s.) elicited responses in coronal gyrus on the same side.
B: 0.3 msec., 10v., 7.5 p.s., anterior suprasylvian gyrus on the same side.
C: 0.3 msec., 10v., 9 p.s., middle ectosylvian gyrus on the opposite side.
D: 0.2 msec., 12v., 9 p.s., middle suprasylvian gyrus on the same side.
Time marker 60 c/s in all. Calibration, 200μv.

somatosensory receiving area (gyr. sigmoid. post.)

(3) Cortical distribution of our response.

According to the results of experiment which was carried out by monopolar leading mainly and by bipolar leading with tip distance of 2-4 mm successively,

our responses were obtained from the wide cortical areas by means of liminal or supraliminal stimulation.

Usually, surface EEG was recorded from the cerebral convexity and in the majority of our cases our responses were recordable from the following cortical areas: anterior, middle and posterior suprasylvian gyrus, coronal gyrus, lateral gyrus, anterior, middle and posterior ectosylvian gyrus and anterior and posterior sigmoid gyrus. Responses were obtained also from fornicate gyrus and piriform gyrus with the bipolar electrode inserted slightly deeper than the cortical surface. Fig. 5 shows an example of cortical distribution of responses by means of single shock. In other words, cortical distribution was diffuse involving somatosensory and auditory receiving areas.

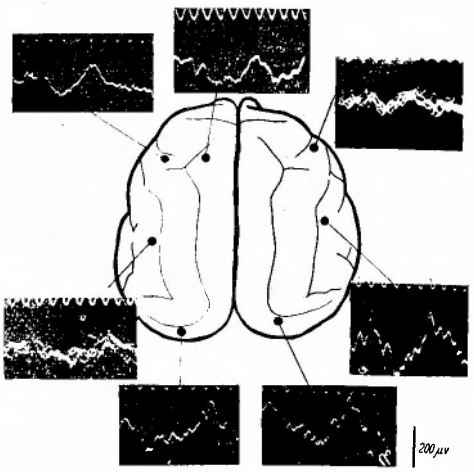

Fig. 5 Distribution pattern of cortical response following single shock of mesencephalic central gray in one and the same case. Stimulation (1 msec., 8 v.). Time marker 60 c/s.

Although appearances of the responses were sometimes apt to depend upon the many experimental conditions, cortical distribution (inclusive of the anterior and posterior areas) was not signifcantly influenced by the stimulating point within the mesencephalic effective region.

(4) Fluctuation of the amplitude.

It is obvious from the previous study of our laboratoy that recruiting response-like EEG changes induced with extrathalamic stimulation occur most easily by about 10 per second frequencies of stimulation.

The recruitment of the responses during repetitive stimulation was not so constant, as seen in the case of recruiting response in anesthetized cats, probably because of the difficult conditions of being unanesthetized (Fig. 4). For instance, during the maintaining stimulation, some responses show already high amplitude to the first stimulation without the marked tendency to augment to successive stimulus (Fig. 4. D), others little or no response to the first with slowly developing recruitment during continuous stimulation (Fig. 4. C., Fig. 7. left) and others occassionally waxing and waning (Fig. 4. B).

These fluctuations of amplitudes were usually most distinct in the main negative waves. Sometimes even in the same case under the same conditions, the different modes of fluctuations were observed in different series of stimulation.

(5) Response time.

Although it was difficult to measure response time exactly, the latency, for instance, was measured from the beginning of the stimulus artifact to the onset of the negative or positive deflection along the base line as well as possible. In one case of single stimulus of mesencephalic central gray matter, latencies of the main

negative waves from the various cortical areas, that is, anterior suprasylvian gyrus, middle ectosylvian gyrus and posterior suprasylvian gyrus bilaterally, were as follows respectively: 50 msec., 40 msec., 70 msec, 82 msec., 70 msec., 56 msec. and more or less different in accordance with the leading cortical areas. Tracing latencies in the total examples as well as possible, those of main negative waves were 30 to 85 msec. (in the majority, 30 to 50 msec.), initial negative waves 3 to 8 msec. and following positive waves 10 to 30 msec. (mostly 12 to 20 msec.). Peak times of the main negative waves were between 50 and 90 msec. and its duration 40 to 70 msec. In case of augmentation of the responses during the repetitive stimulation, fluctuations of the latencies of the main negative waves were generally not so marked as in usual recruiting response.

(6) Our response and various stimulating conditions.

With various intensities and frequencies of stimulation, responses were observed.

a) With increasing of intensity by 2 volts, the appearances of the main negative waves were observed. In the example of Fig. 6 the main negative wave appeared

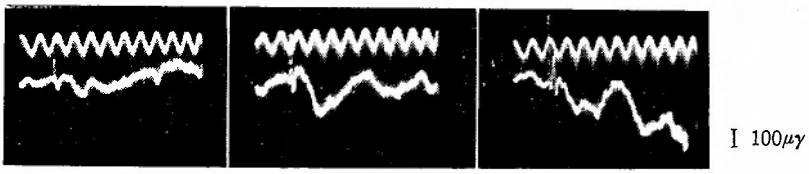

Fig. 6 Cortical response in anterior suprasylvian gyrus to liminal stimulation of mesencephalic central gray. Left: 1 msec., 2 v. middle: 4 v. right: 6 v. Time marker 60 c/s. Notice that main negative wave begins to appear with intensity of 4 v.

at first with stimulation of 1 msec. and 3 or 4 volts. On the other hand with gradual decrease it disappeared with about 3 or 4 volts. In many cases, the liminal threshold to evoke the main negative wave did not necessarily rely upon the stimulated loci within the medial mesencephalon or upon the recorded cortical areas. With increasing supraliminal intensity, not so marked changes in wave forms occurred in most cases, except slight increase in amplitude of positive and negative wave, but sometimes marked increase of positive wave and a little prolongation or shortening of latency of negative wave were seen. We also had an example (Fig. 7), in which responses gradually increasing during repetitive stimulation became constant in amplitude by increasing voltage. But, generally speaking, we could not find in our response the definite relationship between stimulating intensity and waxing-and-waning, which should be observed in typical recruiting response in anesthetized animal according to JASPER (1949). The reason for this may be that response to low voltage stimulation may be covered by the spontaneous EEG in our conditions. With increasing intensity, diffuse cortical distribution was inclined to be more marked.

b) Although it was clearly observed that responses were synchronized with stimulation of frequencies up to 20 or 30 per second, optimal frequency is about 10 per second just as was shown in the previous report from our laboratory. Changes

of frequencies around 10 per second did not greatly influence the amplitude and latency of the main negative wave.

(7) The influence of anesthesia upon our responses.

The investigations about the so called recruiting response with use of muscle relaxants and under unanesthetic state were recently reported but "classical recruiting response" which MORISON and DEMPSEY at first reported was found out in the cats under nembutal anesthesia. In this experiment unanesthetized (restrained) cats were mostly used but in a few cases, in order to compare with the recruiting response, "Ravonal" (sodium 5-ethyl-5 (1-

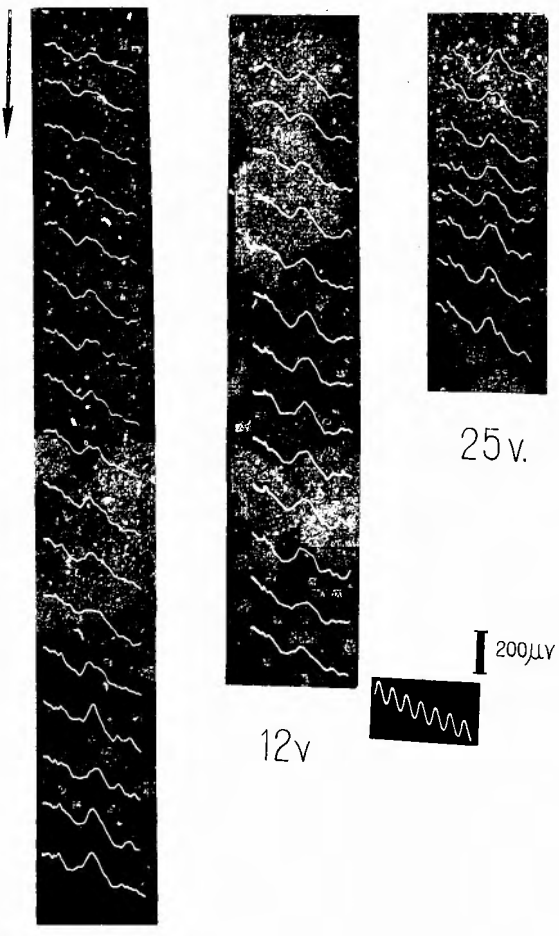

Fig. 7 A case of cortical response when stimulating intensity was increased. Stimulation (0.2 msec., 9 p.s., left: 6 v., middle: 12 v., right: 25 v.) of mesencephalic central gray matter. Lead from middle suprasylvian gyrus. Time marker 60 c/s.

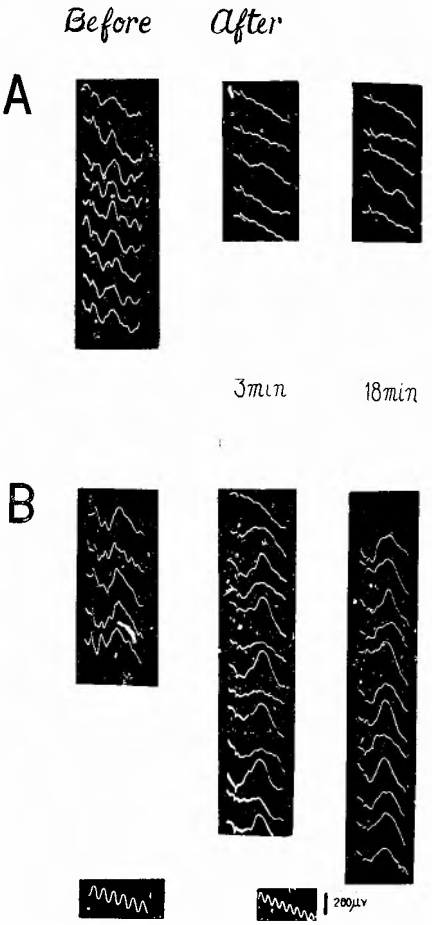

Fig. 8 Our response was depressed when intraperitoneal injection of Ravonal was carried out. A: Our response to stimulation of mesencephalic central gray. B: Recruiting response to stimulation of centrum medianum. Both two responses were led from middle suprasylvian gyrus on the same side. Left: before injection. Stimulation (0.2 msec., 10 v., 9 p.s.) of the above two loci. Middle: 3 minutes after injection of Ravonal 25 mg per kilogram. Stimulation (0.2 msec., 10 v., 8 p.s.). Right: 18 minutes after injection. Stimulation as above. Time marker 60 c/s.

methylbutyl) thiobarbiturate) was used to examine the influence of anesthesia upon our response.

In one and the same cat, after stimulating electrodes were inserted into both mesencephalic central gray matter and centrum medianum of thalamus on the same side, the influences of anesthesia upon each two responses were compared, which were obtained by stimulation of the both loci with the same stimulating conditions and by leading from the same cortical area (in this case the middle part of middle suprasylvian gyrus on the same side) (Fig. 8). Ravonal of 25 mg per kilogram was injected intraperitoneally. 3 minutes after injection, when slight muscular relaxation, miosis, decrease of nocireflex and slow waves sometimes spindles on EEG appeared, on stimulating mesencephalic central gray matter with the same conditions as before anesthesia, responses no longer occurred at all from the cortical areas above described or elewhere.

On the contrary, at this time on stimulating centrum medianum, one of the diffusely projecting thalamic nuclei, responses were elicited markedly to every other stimulus (alternation). Moreover, 18 minutes after injection, at the time of marked slow waves in EEG, muscular relaxation and slow respirations, responses to stimulation of mesencephalic central gray matter still did not occur from each cortical area, while marked response to centrum medianum did. Afterwards, frequencies of stimulation were reduced to about 3 per second but no response to stimulation of mesencephalic central gray matter was obtained from diffuse cortical areas whereas stimulation of the diffuse thalamocortical projection system (centrum medianum) elicited recruiting response. 53 minutes after injection, the cat began to move slightly and awake, and subsequently 35 minutes afterward, with low frequency stimulation of mesencephalic central gray matter responses began to appear.

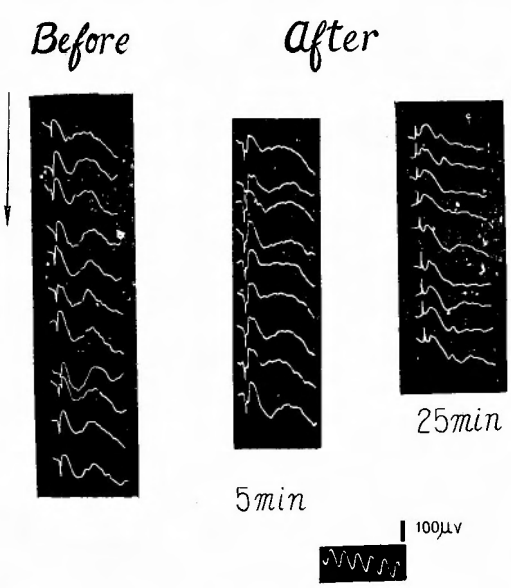

Fig. 9 Our response recorded from posterior suprasylvian gyrus following stimulation (1 msec., 10 v., 8 p.s.) of mesencephalic central gray was depressed by means of intraperitoneal injection of Ravonal. Left: before injection. Middle: 5 minutes after injection of Ravonal 60 mg per kilogram. Right: 25 minutes after injection (with supplement of 60 mg after 22 minutes). Time marker 60 c/s.

Fig. 9 shows the same effect of anesthesia as above. 5 minutes after injection, anesthesia depressed cortical responses to stimulation of mesencephalic central gray matter. Especially the amplitude of the main negative wave decreased and tended to become flat and 25 minutes after injection, entirely disappeared. Initial negative wave seen in this case was almost uninfluenced.

As mentioned above, cortical responses to repetitive stimulation of mesencephalic central gray matter were much more

sensitive than that to stimulation of the diffusely projecting thalamic nuclei for anesthetics such as Ravonal and depressed so markedly.

(8) The influence of the cooling upon our responses.

During the long-lasting experiment with exposure of the brain, the same experimental procedure, if repeated with a certain interval, does not always elicite the same result again. For this many reasons may be considered, above all, cooling and dehydration of the cerebral cortex seemed to influence the appearances of our cortical responses, and here main negative waves were most sensitive and apt to disappear while initial negative waves and positive waves still could be seen. These ill effects disappeared by means of prevention from cooling and dehydration of the brain.

This fact seems to give us a suggestion about the origin of each element of our response.

(B) Electrophysiological connections between mesencephalic central gray matter and various subcortical structures.

Stimulating mesencephalic central gray matter and its adjacent reticular formation and recording responses from depths of the brain, we examined the loci of predilection where the responses were most easily obtained and also the nature of the responses. The responses in depths were not so simple in wave forms and others as compared with the surface responses on account of being more easily influenced by many experimental conditions. Although the descriptions about the subcortical connections from mesencephalic central gray substance had already

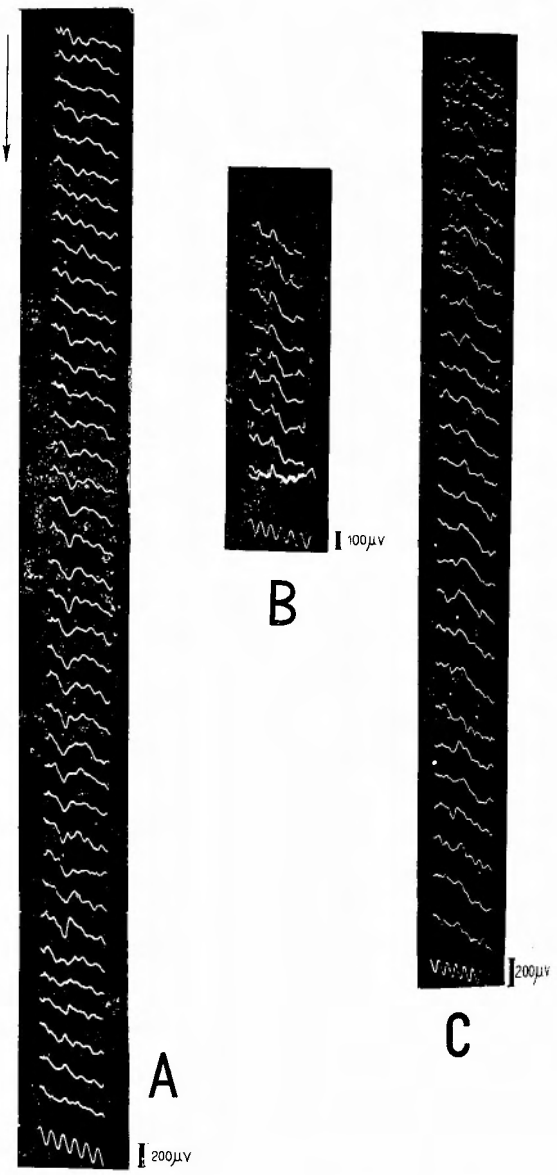

Fig. 10 Responses recorded in depth of the brain by stimulation of mesencephalic central gray matter. A: 1 msec. 8 v., 10 p.s. Response led from the region of nucleus ruber on the same side. Notice slow development of positive deflections during repetitive stimulation. B: 1msec. 15 v., 10 p.s. From mesencephalic reticular formation (just dorsal to nucleus interpeduncularis). C: 0.2 msec., 10 v., 8.5 p.s. From centrum medianum on the same side. Time marker 60 c/s.

ıeen made by ARAKI, SAKATA and MATSUNAGA, the loci in depth of the brain from vhich responses occurred markedly to stimulation of mesencephalic central gray natter in this study were as follows: various parts of midbrain tegmentum (retiular formation, nucl. ruber) ventral parts of thalamus (centrum medianum, nucl. euniens, lamina medullaris externa, neighborhood of nucl. ventralis anterior), zona ncerta, lateral hypothalamus, ventral part of capsula interna, head of nucl. caulatus and nucl. amygdalae lateralis. In addition there seem to be not a few other oci from which responses are more or less recordable, though not ascertained in a ufficient number of cases. The depth responses were elicitable with nearly the same timulating conditions as the surface responses. They were evoked with single shock ır low frequencies of stimulation of about 10 per second given to the midbrain entral gray (Fig. 10. Fig. 11) without or with recruitment (Fig. 10. A).

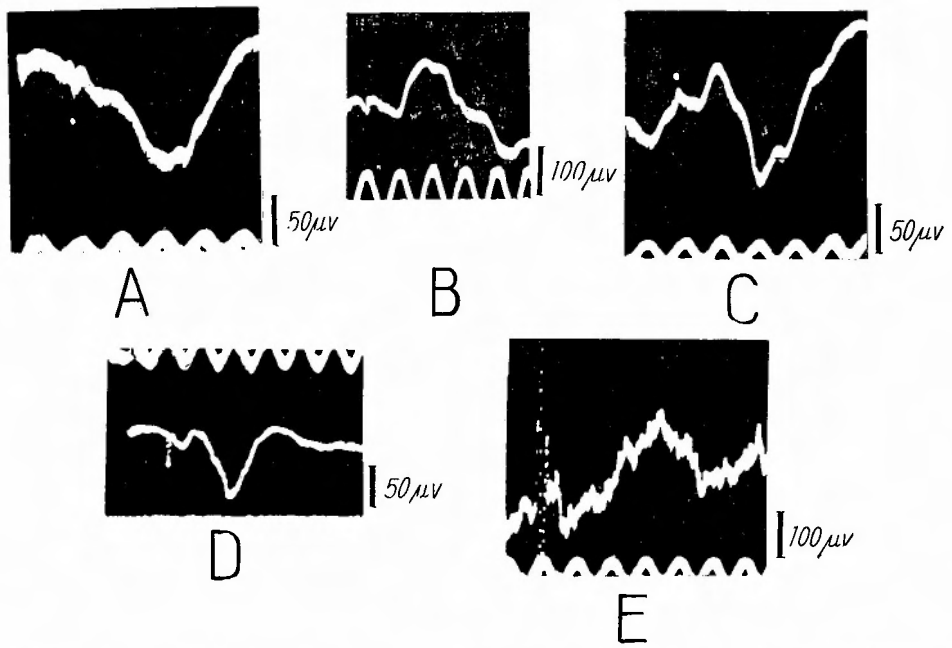

Fig. 11 Subcortical responses to mesencephalic single stimulus. A: Stimulation (1 msec., 8 v.) of mesencephalic central gray. Lead from external medullary lamina. B: Stimulation (0.2 msec., 10 v.) of the same region as above. Lead from centrum medianum on the same side. C: Stimulation (1 msec., 10 v.) of the same region as above. Lead from nucleus reuniens. D: Stimulation (1 msec., 8 v.) of mesencephalic reticular fomation (adjacent to central gray matter). Lead from just below the surface of fornicate gyrus on the same side. E: Stimulation (1 msec. 8 v.) of the same region as above. Lead from internal capsule (close to nucleus entopeduncularis). Time marker 60 c/s in all.

Wave forms were sometimes influenced by leading methods, especially, positions ınd directions of electrodes, but mostly monophasic positive or negative waves in :ase of monopolar leading. Those of subcortical responses, in particular, from the nidbrain reticular formation were mostly steep and their deflections were short in luration time.

It is difficult to measure the exact latency owing to variations in wave forms

but if the latency is measured from the stimulus artifact to the first conspicuous deflection in all cases, it amounts roughly within the range of 5 msec. to 35 msec., but differs according to pick up sites. Namely, subcortical responses in mesencephalic reticular formation and centrum medianum etc. which were closer to the stimulating loci (midbrain central gray), had generally shorter latencies than those in head of nucl. caudatus and others which were remote. Latencies of the former were about 5 to 20 msec., and the latter about 10 to 30 msec. Those of responses recorded from mesencephalic reticular formation were in most shorter than 10 msec. After all, latencies of subcortical responses generally seemed to be shorter, at least never longer, than those of cortical negative waves.

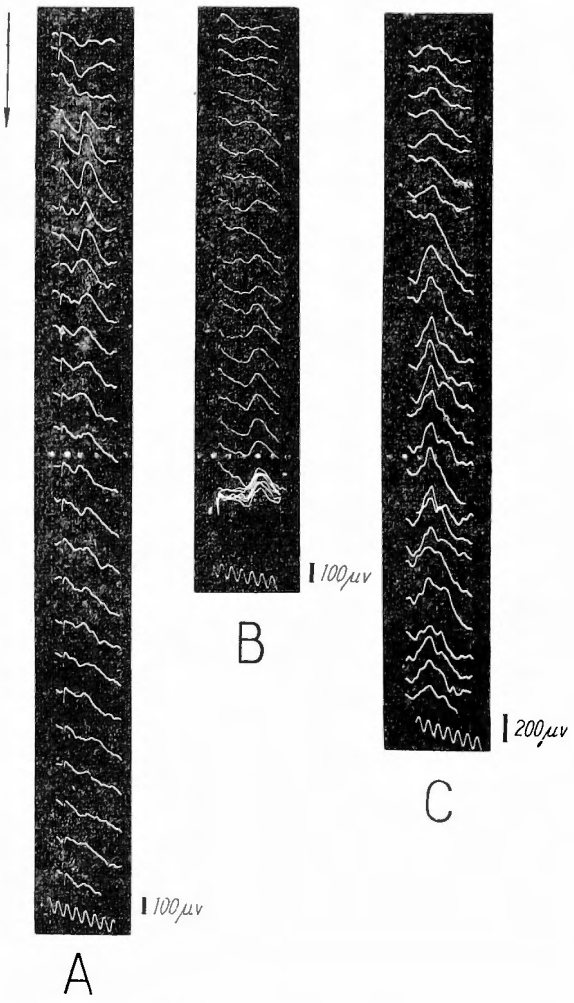

Fig. 12 Cortical responses induced by stimulation of the diffusely projecting thalamic nuclei.
A: Stimulation (0.2 msec., 10 v., 8.5 p.s.) of centrum medianum. Lead from anterior sigmoid gyrus on the opposite side. B: Stimulation (0.5 msec., 6 v., 9 p.s.) of nucleus reticularis. Lead from posterior suprasylvian gyrus on the opposite side. C: Stimulation (0.5 msec., 10 v., 9 p.s.) in the region of nucl. ventalis anterior. Lead from posterior sigmoid gyrus on the opposite side. Time marker 60 c/s.

(C) Cortical responses to stimulation of thalamus and other structures.

In comparison with our cortical responses to stimulation of mesencephalic central gray matter, cortical responses to stimulation of the diffusely projecting thalamic nuclei, thalamic sensory relay nuclei and others were examined in unanesthetized animals. Also in our conditions, cortical responses to stimulation of the diffusely projecting thalamic nuclei were confirmed to possess various properties of recruiting response described in literature (Fig. 12), i. e. they showed diffuse cortical distributions, main negative waves, optimal stimulating frequencies of about 10 per second, waxing and waning which could be seen frequently, long latencies with fluctuations and tendency to become more typical by anesthesia.

Widespread short latency (about 15 msec.) responses were gained to stimulation of nucleus ventralis anterior (Fig. 12).

On the other hand, the latencies of negative waves of recruiting response in our conditions were 30 to 70 msec., which were nearly the same as those to stimulation of mesencephalic central gray substances, but the development of the former response was in some cases atipycal in that the response was slowly recruited after the end of a few repetitive stimuli or it was elicited maximally by the first stimulus. Although these variations were not strange and probably owing to the differences of experimental conditions, this made us feel that the so called recruiting response should be understood in wider sense than the classical recruiting response originated by MORISON and DEMPSEY.

When medial lemniscus of midbrain or nucleus ventralis posterolateralis of thalamus, namely, sensory system was stimulated, responses occurred which had short latencies and wave forms consisting of, first, positive, next, spike-like short durable negative and then positive phases in the localized sensory receiving areas as described in the literature. These responses seemed to be different in many respects from the so-called recruiting response and our response to stimulation of mesencephalic central gray matter.

DISCUSSION

It was confirmed that in unanesthetized (restrained) cat mesencephalic central gray matter, especially its ventral portion, and its adjacent reticular formation, rostrocaudally from oculomotor nucleus to trochlear nucleus have electrophysiological connections with the diffuse cerebral cortex and subcortical structures. The response by these ways will be discussed in comparison with so called recruiting response to stimulation of the diffusely projecting thalamic nuclei and with some other responses described in the literature and then some considerations will be made from the viewpoint of coma.

a) Comparison with recruiting response.

Since MORISON and DEMPSEY (1942) had first described recruiting response, much information about it was advanced by JASPER (1949) and others and recently the response was reported to occur under non-anesthesia with the use of muscle relaxants. But it is not easy to decide whether we can apply the term of recruiting response to our response or not, in considering that with more advancing and developing of the information about recruiting response some different views exist among investigators.

Though it has been thought to be reasonable that the most characteristic aspect of recruiting response is resemblance to spindle burst during anesthesia, recently reported is the fact that spindle burst resembles in a certain respect augmenting response, which occurs by stimulation of specific thalamic nuclei, rather than recruiting response.

If the term "recruiting response" is to be used only for response elicited in the diffuse cortical areas by stimulation of the diffusely projecting thalamic nuclei, of course we can not call our response, which is induced with stimulation of the mesencephalic central gray matter in this experiment, by the name of recruiting

response. But some comparison will be made of our response with recruiting response from the results obtained in this study.

Recently, J. M. BROOKHART and A. ZANCHETTI (1956), discussing the difference between recruiting response and augmenting response, defined "pure recruiting response" as follows: 1) generalized cortical distribution 2) slow development with little or no response to the first stimulation 3) latency in excess of 15 msec. 4) minimal initial positivity. Validity of each of these criteria in our response will be considered in detail.

(1) Cortical distribution of the response was found by means of monopolar and bipolar leading to be diffuse on the cortical convexity including somatosensory and auditory receiving areas without marked local predominance. It is to be noticed that stimulation of either diffusely projecting thalamic system or mesencephalic central gray matter (under the same conditions) in the same case could elicite each typical response in the same cortical leading area (reference to A, (7) of Results). This fact shows that both of these responses have, at least in part, common cortical distributions.

(2) Slow development. In regard to development of recruiting response during repetitive stimulation of the thalamus, JASPER proved that it differed depending on modes of leading and stimulation, that is, changes of stimulus intensity and leading area sometimes induced constant amplitude response and sometimes waxing and waning response, and consequently development of recruitment had a certain causal relation with conditions of stimulation and leading in anesthetized cat. However, in one or two reports in the literature responses which show the maximum amplitude from the beginning of stimulation in stead of slow development are described as recruiting response. In our experiment in which the diffusely projecting thalamic nuclei were stimulated in unanesthetized animals, atypical recruiting response without slow development were frequently observed by usual stimulation.

On the other hand, stimulation of mesencephalic central gray matter sometimes elicited slowly developing, or occassionally waxing-and-waning response, but more often remarkable response to the first stimulation. And these different types of response sometimes changed from one to another mutually under the same conditions (due to unknown factors). In our response, causal relations between conditions of stimulation or leading and response types as described in recruiting response of anesthetized animals were not so definite with a few exceptions (Fig. 7).

Thus from the common or uncommon occurrence of typical recruitment it may not be concluded that our response essentially differs from so-called recruiting response to stimulation of the diffusely projecting thalamic nuclei. Of course, recruitment or gradual increase of amplitudes is a phenomenon due to facilitation of excitation in the central nervous system, which is seen also when some loci other than diffusely projecting thalamic nuclei are stimulated (GLOOR, 1955 and others).

(3) Although latencies varied more or less according to conditions of stimulation and leading, the high voltage main negative wave showed latency of 30 to 85 msec. (mostly 30 to 50 msec.) In the literature latency of negative wave of

recruiting response was reported as follows: MORISON and DEMPSEY: 20 to 35 msec., MAGOUN et al: 15 to 60 msec., JASPER: 5 to 40 msec. In this study latency of recruiting response obtained under non-anesthesia by stimulation of the diffusely projecting thalamic nuclei was 30 to 70 msec., roughly similar to that obtained by stimulation of mesencephalic central gray with exception of short latency (about 15 msec.) diffuse response to stimulation of nucl. ventralis anterior. By the way, duration of negative wave of our response was 40 to 70 msec. and that of recruiting response according to JASPER et al, MORISON and DEMPSEY was 30 to 50 msec. Fluctuations of latencies of recruiting response are already known (JASPER et al 1953, AJMONE-MARSAN 1956).

(4) Minimal initial positivity. Of our response main negative wave is most prominent with little or no positive wave. Therefore monophasic form occurs most frequently. This is similar to that of recruiting response to stimulation of the diffusely projecting thalamic nuclei in previous reports or in this experiment. In some cases short latency negative response localized in posterior sigmoid gyrus and its neighborhood (somatosensory receiving areas) was obtained.

From the above it is considered that our cortical response in unanesthetized cat does not necessarily stand against recruiting response. Strictly speaking, it is not the same as recruiting response in JASPER's report in that slow development of our response could not be easily controlled by conditions of stimulation and recording but this does not seem absolutely necessary. Otherwise cortical responses to low frequency repetitive stimulation of mesencephalic central gray matter and its adjacent reticular formation may not be different from recruiting response in an ordinary sense. Still more, as described later, in considering the fact that mesencephalic central gray has functional connections with the diffuse thalamocortical projection system, it is possible to assume that both responses may be essentially the same neurophysiological phenomenon. However, it is well known that classical recruiting response to stimulation of the diffusely projecting thalamic nuclei appears so markedly under anesthesia and is difficult to be elicited in very alert or excited animals. Many descriptions have been made about relations between recruiting response and anesthesia. KING (1954) stated that the anesthetics such as chloralosane, pentobarbital and penthotal increased the amplitude and decreased the threshold of recruiting response while they suppressed EEG arousal induced with stimulation of mesencephalic reticular formation. Comparing the effect of anesthesia (Ravonal) upon recruiting response to thalamic stimulation with that upon our response to mesencephalic stimulation, we could find remarkable difference in sensitivity to anesthetics. Namely, the former, i. e. recruiting response did not disappear at all and became rather more typical and marked, though it showed slight decrease of optimal frequency of stimulation. On the other hand, the latter, i. e. our response to mesencephalic stimulation decreased its amplitude and then disappeared entirely till awakening, even with use of greatly lowered stimulating frequencies, at the anesthetic stage in which recruiting response was easily elicitable to thalamic stimulation. Thus our response was suppressed more sensitively by Ravonal. That also

in both responses from the same cortical area in the same animal such a difference was seen, makes us suppose different mechanisms of these two responses but we cannot immediately conclude so for following reasons. As mesencephalic central gray matter seems to be connected with the diffuse thalamocortical projection system with relatively short latency response according to our experiment, both responses take probably the same subcortical paths to reach the cerebral cortex, while according to MAGOUN the brain stem activating system including mesencephalic reticular formation is sensitive to barbiturates and functionally suppressed easily and therefore different effects of anesthesia upon the two responses may result, though the essential natures of the responses are not necessarily different.

b) Electrophysiological connections of mesencephalic central gray matter with subcortical structures.

The stimulations of mesencephalic central gray matter induce responses clearly in unanesthetized animals in wide subcortical structures: midbrain tegmentum, hypothalamus, ventral portion of thalamus (in particular, a part of the diffuse thalamocortical projection system), head of nucleus caudatus, ventral part of internal capsule, lateral amygdaloid nucleus. Besides, ARAKI, SAKATA and MATSUNAGA proved recruiting response-like EEG changes in medullary central gray, by stimulation of mesencephalic central gray matter. MAGOUN et al (1951) reported that under chloralosane or nembutal anesthesia, medullary or mesencephalic reticular formation stimulation elicited responses in midbrain tegmentum, ventromedial thalamus, subthalamus, hypothalamus and capsula interna. Anatomically, tracts from midbrain central gray to midbrain tegmentum, hypothalamus and a part of thalamus (nucleus parafascicularis, centrum medianum, et al) were found (F. H. JOHNSON, 1953).

Subcortical responses were synchronized with each repetitive stimulus of about 10 per second or single shock given to mesencephalic central gray matter and its surrounding structures. Those in rostral mesencephalon or posterior thalamus have relatively short latencies of about 10 msec. sometimes with marked recruitment. Though it is difficult to measure latencies and wave forms exactly, generally maximum deflections have latencies of about 5 to 30 msec., which are at least not longer than those of cortical responses. Particularly, latencies of responses in midbrain reticular formation and nucl. ruber, etc. are shorter than those in head of nucleus caudatus and capsula interna. Therefore, these subcortical structures may be thought to be relay stations of excitatory transmission from mesencephalic central gray matter to cerebral cortex. As latencies of responses in rostral mesencephalic reticular formation are sufficiently short as compared with those of our cortical responses, especially of recruiting response to stimulation of the diffusley projecting thalamic nuclei, it may be expected that connecting paths, at least a part of them, from mesencephalic central gray to diffuse cortical areas may run through the diffuse thalamic projection system. Long latencies of diffuse cortical response to stimulation of mesencephalic central gray matter probably may be due to the paths via diffuse thalamocortical projection system. MAGOUN, LI, CULLEN and JASPER investigated the structures where synaptic delay of recruiting response occurred. The fact that our

response is much more sensitive to anesthesia and rather hard to show typical waxing and waning as compared with pure recruiting response, may be attributed to interposition of many neural paths from central gray matter to the diffuse thalamocortical projection system. It may be supposed that because of indirect bombing to the diffuse thalamocortical projection system by impulses via these successive interpositive neural paths, rhythmical excitatory recruitment within this system may not occur so typically as by direct bombing within the diffuse thalamocortical projection system. Thus cortical response to stimulation of central gray matter should be exactly named as modified recruiting response as opposed to pure recruiting response. But recruiting response and our cortical response may not be different in their essential nature.

However from the fact that responses with relatively long latencies of about 30 msec. are induced in rostral subcortical extrathalamic structures, i.e. head of nucleus caudatus, a part of internal capsule and amygdala, and also from the results of experiments of thalamic destruction by MAGOUN (1951), possibility of occurrence of cortical response via extrathalamic route from mesencephalic central gray matter to diffuse cortical areas cannot be denied. In other words, two routes, intrathalamic and extrathalamic, should be assumed.

c) Relation to the brain stem activating system.

STARZL, TAYLOR and MAGOUN (1951) reported that under relatively light anesthesia with chloralosane or nembutal, stimulation of medial mesencephalon induced best generalized cortical desynchronization. They stated that reliable desynchronizing effect was obtained from the stimulation of mesencephalic reticular formation, but not reliable desynchronizing effect was induced by that of other structures including probably mesencephalic central gray matter. They then added that distribution of the cortical potentials evoked by single shock stimulation of the brain stem reticular activating system, either in the midrain or medulla, was widespread to a degree, but response in the frontal pole was more remarkable, which was synchronized with repetitive stimulation up to 8-10 p. s., while response in the posterior pole was greatly variable, augmented by serially repetitive stimuli and had different wave form from that in the anterior. In our responses, such differences according to leading cortical areas were not found. Namely, their appearances were uniformly diffuse with wave-like form and showed no local predominance.

d) Relation to secondary response.

Secondary response was found under deep barbiturate anesthesia from widespread cortical areas by means of sciatic stimulation by FORBSE and MORISON (1936). Afterwards, PURPURA (1955) stated that under deep barbiturate anesthesia he could reproduce it by single shock stimulation of mesencephalic reticular formation. According to him, it represented the maximal positive wave in the anterior part of lateral gyrus while response in posterior pole of the cortex was thought to have spread from anterior.

Our cortical response to mesencephalic central gray stimulation differs from secondary response in anesthetic influence, cortical distribution, wave forms and

others.

e) Discussing conclusively, in our experiment on unanesthetized but resting animals, by means of low frequency repetitive stimulation of mesencephalic central gray and its adjacent reticular formation, electrical activity of widespread cerebral cortex was elicited in synchronization with stimulating frequencies.

Moreover, in consideration of the existence of abundant cortical and subcortical connections, it can be presumed that mesencephalic central gray may influence the functions of the whole brain and abnormal discharges occurring at this mesencephalic central gray and its neighborhood may affect the whole brain and thus may play an important role in the mechanism of coma occurring immediately after head injuries.

CONCLUSION

1. On observing recruiting response-like EEG changes induced with stimulation of mesencephalic central gray matter of unanesthetized cat reported previously by ARAKI, SAKATA and MATSUNAGA, this brain portion was confirmed to have many connections with diffuse cortical and subcortical structures.

2. As to cortical responses obtained in this experiment, they were discussed in comparison with recruiting response to stimulation of the diffuse thalamocortical projection system, and seemed analogous in some respects to the latter. It is worthy of note that in the experiment under anesthesia, the matter changes entirely.

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和 文 抄 録

中脳中心灰白質と大脳皮質との電気生理学的結合について

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先に荒木，坂田，松永の行つた無麻酔猫に於ける中脳中心灰白質附近の刺戟実験により誘発せられたrecruiting response 様現象について更に観察した結果，此脳部分が広範な大脳皮質及皮質下諸部と豊富な結合関係を有する事を再確認した．又此際見られる皮質レスポンスについて，所謂recruiting responseと比較検討を試み，少からざる面に於て此と同義的な意味を有するものであろう事を推論した．併し，麻酔下の実験では，このような recruiting response 様の反応が出なくなる事は注目さるべきである．